Contains Nonbinding Recommendations

Draft - Not for Implementation

Draft Guidance for Industry and FDA Staff

The Review and Inspection of Premarket Approval Application Manufacturing Information and Operations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
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Public Comment

Comments and suggestions on this draft guidance document should be submitted within 90 days of the date it became available by publication in the *Federal Register*. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Alternatively, submit electronic comments to http://www.fda.gov/dockets/ecomments. Identify all comments with the docket number listed in the notice of availability from the *Federal Register*.

Direct questions regarding this document to Mr. Timothy A. Ulatowski, CDRH, at 240-276-0100, or email timothy.ulatowski@fda.hhs.gov.

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Center for Devices and Radiological Health

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Office of In Vitro Diagnostic Device Evaluation and Safety

Preface

Additional Copies

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The Review and Inspection of Premarket Approval Application Manufacturing Information and Operations

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

Introduction

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) amended the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq.) (the Act) to allow for the collection of user fees for the review of certain marketing applications. A portion of the fee collected for premarket approval applications (PMAs) will help cover the costs associated with the review of the PMA manufacturing section information and the inspection of the manufacturing facilities. In a letter to Congress that accompanied the user fee legislation, the Secretary of Health and Human Services committed to "improve the scheduling and timeliness of preapproval inspections."[1]

[1] This letter can be found at: www.fda.gov/cdrh/mdufma/pgoals.html

This guidance explains for applicants the process involved with the review of a PMA manufacturing section and inspection of the manufacturing operations described in the manufacturing section. This guidance is also generally applicable to the process involved with the review of manufacturing information in certain PMA supplements. FDA believes that the procedural information outlined in this document should help applicants and FDA schedule and complete their work in a timely manner.

The following will be addressed in this guidance:

- The sequence of events as the Office of Compliance (OC) or the Office of *In Vitro* Diagnostic Device Evaluation and Safety (OIVD) reviews the manufacturing section of a PMA;
- The administrative process and projected timeframes involved with each step; and
- How the inspection of a manufacturing facility fits into the approval process.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

We believe we should consider the least burdensome approach in all areas of medical device regulation. This guidance reflects our careful review of the relevant scientific and legal requirements and what we believe is the least burdensome way for you to comply with those requirements. However, if you believe that an alternative approach would be less burdensome, please contact us so we can consider your point of view. You may send your written comments to the contact person listed in the preface to this guidance or to the CDRH Ombudsman. Comprehensive information on CDRH's Ombudsman, including ways to contact him, can be found on the Internet at http://www.fda.gov/cdrh/ombudsman/

Scope

This guidance explains the administrative process used by OC or OIVD to review a PMA's Quality System (QS) regulation (21 CFR 820) information. OC has already published guidance, entitled "Quality System Information for Certain Premarket Application Reviews," which identifies the QS regulation information an applicant should include in the PMA manufacturing section.[2] In addition, two corollary documents discuss generally the FDA review procedures and clock for PMAs, including the review of QS regulation information and the inspection process. One document is entitled, "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Performance

[2] This guidance is available at: www.fda.gov/cdrh/comp/guidance/1140.pdf

Assessment."[3] The other guidance is entitled, "Premarket Approval Application Modular Review."[4] This guidance does not address premarket notification (510(k)) submissions because a premarket inspection is not ordinarily conducted for this type of premarket submission. Within the text of this guidance are additional exclusions related to the types of premarket submissions not covered by this guidance.

Premarket Approval Applications

The usual path to approval of a device is submission of a PMA, which may be traditional or modular, and expedited or non-expedited.[5] When seeking premarket approval for your device, you may select the appropriate type of PMA submission based on the following:

1. Traditional PMA

In this PMA format, you would submit all the elements required for a PMA, e.g., complete scientific and technical information about the device, manufacturing information, non-clinical study information, and statistically valid and reliable data from clinical studies, at the same time in a single application, so we can determine whether there is a reasonable assurance that the device is safe and effective for its intended use. For guidance on the type of information needed for FDA to file your PMA, see "Premarket Approval Application Filing Review."[6]

2. Modular PMA

This PMA format consists of sections or modules submitted separately that together become a complete application. Each module includes elements, tests, or other information that constitute a component of a complete PMA, such as manufacturing information or clinical data. For more information on the Modular PMA Program, see the guidance entitled "Premarket Approval Application Modular Review."[4]

3. Expedited PMA (Traditional and Modular)

We give priority to PMAs for devices under certain circumstances. The Office of Device Evaluation (ODE) and OIVD determine, using criteria defined in section 515(d)(5) of the Act, whether a PMA qualifies for expedited status. For more information on expedited

[3] This guidance can be found at: www.fda.gov/cdrh/mdufma/guidance/1218.html
[4] This guidance can be found at: www.fda.gov/cdrh/mdufma/guidance/835.html
[5] The Product Development Protocol, and, for devices that meet narrow criteria, the Humanitarian Device Exemption, provide alternate approval mechanisms. However, these applications are not subject to the MDUFMA performance goals and are not discussed in this guidance.
[6] This guidance can be found at: www.fda.gov/cdrh/ode/guidance/297.html

PMAs, see the guidance entitled, "Expedited Review of Premarket Submissions for Devices."[7]

B. Types of PMA Supplements

You must submit a PMA supplement for review and approval if you make a change affecting the safety or effectiveness of a device for which you have an approved PMA. (21 C.F.R. 814.39(a)). Some changes do not require a supplement and some changes may be made using alternative forms of submission, as specified in FDA regulations. MDUFMA defines three types of PMA supplements. These are panel-track supplements, 180-day supplements, and real-time supplements.

Panel-track and 180-day supplements may include manufacturing information. If so, OC or OIVD will review the information and an inspection may be required, depending on the proposed change. When both a review of manufacturing information and an inspection are needed, the review process and timelines described in this guidance generally apply.

Typically, there are no inspections associated with the following types of PMA submissions so they will not be addressed in this guidance:

- Real-time supplements;
- 30-day notices
- 135-day supplements
- Special PMA Supplements-Changes Being Affected
- Express PMA supplements
- PMA annual reports

1. Panel-track Supplements

Section 737(4)(B) of the Act, which was added by section 102 of MDUFMA, defines a "panel-track supplement" as "a supplement to an approved premarket application or premarket report under section 515 that requests a significant change in design or performance of the device, or a new indication for use of the device, and for which substantial clinical data are necessary to provide a reasonable assurance of safety and effectiveness." (21 U.S.C. 379i (4)(B)).

As described in previous guidance, FDA interprets this provision to generally require a panel track supplement for those changes that require the agency to publish a new summary of safety and effectiveness (SSED).[8] Under 21 C.F.R. 814.39(c), supplements that trigger the requirement for a new SSED are those:

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[7] This guidance can be found at: www.fda.gov/cdrh/mdufma/guidance/108.pdf

[8] *See* "Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and

"…submitted for new indications for use of the device, significant changes in the performance or design specifications, circuits, components, ingredients, principles of operation, or physical layout of the device, or when otherwise required by FDA."

Although this section of the PMA regulation provides FDA with discretion as to the type of supplement that should be submitted, the agency has traditionally used this part of the PMA regulation to define when a panel-track supplement is necessary. You should submit a panel-track supplement for:

- a new indication for use (i.e., patient population/disease state); or
- a change in device design or performance that could significantly affect clinical outcome.

A panel-track supplement for the second type of change may require the submission of manufacturing information and an inspection.

Similar to original PMAs, we give priority review to panel-track supplements meeting the criteria defined in section 515(d)(5) of the Act. Therefore, in the discussion below, references to expedited and non-expedited PMAs include expedited and non-expedited panel-track supplements.

2. 180-Day Supplements

Under section 737(4)(C) of the Act, a "180-day supplement" is defined as:

"a supplement to an approved premarket application or premarket report under section 515 that is not a panel-track supplement and requests a significant change in components, materials, design, specification, software, color additives, or labeling." (21 U.S.C. 379i(4)(C)).

FDA believes the above definition closely corresponds to the type of supplement FDA has historically treated as a "180-day supplement."[8] Thus, you should submit a 180-day supplement for a significant change involving:

- the principle of operation;
- the control mechanism;
- the device design or performance;
- the labeling; or

Fees for Combination Products; Guidance for Industry and FDA." This guidance can be found at: www.fda.gov/cdrh/mdufma/guidance/1201.html.

- new testing requirements or acceptance criteria.

For the types of changes listed above, clinical data for the original device must still be applicable to the modified device in order for the change to be submitted as a 180-day supplement. That is, a 180-day supplement, rather than a new PMA, is appropriate when a demonstration of reasonable assurance of safety and effectiveness for the modified device either does not require a new clinical trial to be conducted or requires only limited clinical data. A 180-day supplement involving changes to the design or manufacturing may require submission of manufacturing information and an inspection.

C. The Review Process in Brief

The premarket review process begins when the applicant submits six copies[9] of the PMA or PMA supplement to the CDRH Document Mail Center (DMC) in ODE. Upon receipt, OC or OIVD will review the PMA's manufacturing section. OC or OIVD will request an inspection of the facility if one is needed. There may be more than one manufacturing facility for an original PMA and a facility may be a domestic or foreign site.

Following an inspection, OC or OIVD will receive and analyze the establishment inspection report for the manufacturing facility. OC or OIVD will then make a recommendation to ODE on the status of the quality system for the facility.

This guidance describes the timeframes within which these activities should be completed so the MDUFMA performance goals for review of the application type can be met. Significant deficiencies in the manufacturing information and/or manufacturing operations may result in more than one cycle of review. Flow charts depicting the PMA manufacturing section review and inspection timelines are provided in Attachment A.

FDA Review of the PMA Manufacturing Section, and the Inspection Process

A. What procedure does FDA use to review a PMA manufacturing section?

When the PMA arrives at the ODE/DMC, the DMC processes the application as follows:

1. Logs in and tracks the submission.
2. Assigns due dates for the CDRH offices based on the date of receipt, e.g., 180 days after receipt.
3. Alerts the ODE Program Operations Staff (POS) of the incoming PMA.
4. Sends one complete copy of the PMA to OC Field Operations Branch (OC/FOB) within 7 calendar days of receipt.
5. Files one copy in the DMC.
6. Further processes the application administratively, prepares a transmittal coversheet, and forwards the document to the appropriate ODE review division or OIVD.

[9] See 21 CFR 814.20(b)(2).

When OC/FOB receives its copy of the PMA, it processes the document as follows:

1. OC/FOB assigns an internal tracking number for the PMA, establishes a due date for the OC or OIVD review of the manufacturing information, and generates a transmittal coversheet.

2. The coversheet and the PMA are delivered to the appropriate enforcement division in OC, or to OIVD. If clinical data are submitted in the PMA, OC/FOB forwards the clinical section to the OC Division of Bioresearch Monitoring (DBM) for review.

   Note: The review and processing by DBM will be addressed in separate MDUFMA guidance.

3. OC/FOB alerts the district office associated with a domestic manufacturing site identified in the PMA as to the receipt of the application. OC/FOB requests a response from the appropriate FDA district office within 7 calendar days regarding the inspection history of the manufacturing site. If there are multiple facilities involved in the manufacturing process, OC/FOB will notify all relevant districts.

   The district typically determines the following types of information concerning the manufacturing site from its records:

   a. the date of last inspection;
   b. classification of the last inspection report; and
   c. the similarity of the products inspected to the PMA device and similarity of the manufacturing operations inspected by FDA to those used for the PMA device under review.

   Once the information is received from the district office OC/FOB forwards the information to the assigned OC enforcement division, or to OIVD.

4. OC serves as the district office for any foreign facility. OC, with input from OIVD when necessary, determines whether a foreign manufacturing facility requires an inspection based on the same information noted in item 3 above.

   For foreign sites, OC/FOB notifies the Office of Regional Operations (ORO), Division of Field Investigations (DFI), International Operations Group (IOG) of a pending assignment. ORO/DFI/IOG coordinates the foreign site inspections for the FDA field staff. A provisional inspection assignment for a foreign facility is transmitted from OC/FOB to ORO/DFI/OIG early in the review process (see Attachment A). This early assignment is done before completion of the manufacturing section review because foreign inspections take longer than domestic inspections to organize and complete due to scheduling, travel logistics, and the need for coordinating with foreign governments and the U.S. State Department. The longer organization time for a foreign inspection enables the assigned OC enforcement

division or OIVD to substantially review the PMA manufacturing section and to cancel the inspection if there are major deficiencies.

5. OC or OIVD should complete its review of the PMA manufacturing section within the time frames indicated below in Table 1.[10]

Table 1

TYPE OF PMA APPLICATION	MANUFACTURING SECTION REVIEW TIMEFRAME
Non-Expedited Traditional	30 calendar days
Expedited Traditional	20 calendar days
Non-Expedited Modular	30 calendar days when submitted with final module; up to 90 days if submitted prior to final module
Expedited Modular	20 calendar days when submitted with final module; up to 90 days if submitted prior to final module
180-Day Supplement	30 calendar days
Amendment	20 or 30 calendar days depending on type of PMA amended

B. What happens when OC or OIVD completes its review of the PMA manufacturing section?

The OC or OIVD reviewer (with supervisory concurrence) may: (1) recommend that the manufacturing section is acceptable or (2) prepare a deficiency letter identifying significant deficiencies and requesting additional information from the applicant. The OC or OIVD reviewer will also determine, with supervisory concurrence, whether an inspection is required.

1. If OC or OIVD determines that the PMA's manufacturing section is significantly deficient, the applicant should expect to receive a deficiency letter identifying the specific information to submit to allow FDA to complete the review of the manufacturing section. The OC or OIVD reviewer should communicate in real-time with the applicant to clarify the number and type of deficiencies in a deficiency letter. If there are only a few minor deficiencies, these will likely be handled solely by phone. An extended response time to a deficiency letter or to a phone call for more information, or a delay in your submission of substantial additional manufacturing data, may significantly delay the completion of the initial review. Submission of a response to a deficiency letter will begin a new 20, 30, or up to 90 day manufacturing section review timeframe depending on the type of application. (See Table 1).

[10] Time frames for the QS/GMP review begin one day after FOB receives the PMA document from the DMC.

2. If the review of the manufacturing section is substantially complete and there are no deficiencies in the manufacturing section, or if the deficiencies have been adequately addressed through phone calls or additional submissions, OC or OIVD will evaluate the district office's inspection history of the domestic facility. If OC or OIVD determines that FDA should conduct a QS/GMP inspection, OC/FOB will initiate an assignment with ORO for a domestic inspection. OC/FOB will also confirm that the already initiated foreign inspection assignment should proceed.

3. It is expected the PMA applicant is ready for inspection at the time of the filing of the PMA application unless the applicant states in the PMA that it is not ready. The District (or OC for a foreign facility) should contact the facility's management to alert them to the pending inspection. At that time, the applicant should confirm that the facility is ready for inspection. The manufacturing process should be in operation by the time the inspection is conducted.

4. OC/FOB plans to cancel the inspection assignment under the following circumstances: if the PMA is not filed; ODE or OIVD issues a major deficiency, not approvable, denial, or withdrawal letter; or, the applicant communicates to FDA that the manufacturing site is not ready for inspection.

   If the facility is not ready for inspection, the District (or OC for a foreign facility) will ask the applicant to send a letter to the District or OC, signed by the most responsible person at the firm, indicating that they are not ready for inspection, the reason for not being ready and when they expect to be ready. This letter will be made part of the PMA record.

   The applicant should alert CDRH in advance of when the facility will be ready for inspection. OC/FOB will then reissue an inspection assignment.

C. How much time does the FDA allow for a PMA QS/GMP inspection?

Domestic Inspections:
FDA field staff should complete the inspection within 45 calendar days after receipt of the inspection assignment from OC or OIVD.

Foreign Inspections:
FDA field staff should complete the inspection within 60 calendar days after receipt of the inspection assignment. As noted, foreign travel requires additional time for scheduling, travel logistics, and for coordinating with foreign governments and the U.S. State Department.

An additional 30 calendar days are allotted for the field staff to write and forward a PMA application establishment inspection report to FOB for both domestic and foreign inspections.

D. What happens after the establishment inspection report (EIR) is completed by the field staff?

FDA expects that a manufacturing facility will be in compliance with the requirements of the QS regulation. For domestic inspections, when the inspection identifies deviations, the deviations are limited to the PMA device and do not extend to other devices manufactured in the facility, the relevant FDA district will send the completed EIR and supporting documentation to FOB. If there are significant deviations, OC or OIVD will issue a deficiency letter within 30 calendar days for a non-expedited (traditional or modular) PMA and 20 days for an expedited PMA.

If the QS regulation deviations also apply to marketed products and are violations warranting official action, the District may issue a Warning Letter or Untitled Letter. If the FDA response to deviations is in the form of a Warning or Untitled Letter, the letter will issue within the agency timeframe for these types of letters. If more than one District and manufacturing site is involved, or if the letter contains charges in addition to QS regulation violations, the District will generally forward the letter for review and issuance to OC or OIVD. The applicant should respond to the FDA office issuing the letter within the timeframe noted in the letter. OC/FOB is informed of the issuance of a Warning or Untitled Letter by the District.

For foreign facilities OC or OIVD will also issue a deficiency letter, Warning or Untitled Letter depending on the scope of the deviations. A Warning Letter, whether issued by the District, OC or OIVD, will inform the addressee that no approval for a pending PMA will issue until the QS regulation deficiencies are corrected. The applicant should respond to the FDA office issuing the letter.

OC/FOB will notify ODE POS when the manufacturing operation is not satisfactory (e.g., based upon OC concurrence with the District's recommendation, deficiency letter issued, or Warning/Untitled Letter issued) and recommend that the PMA approval should be withheld, so that POS can make the appropriate entry into the CDRH document tracking database. If ODE or OIVD has completed its review of the PMA and the PMA otherwise warrants an approval or approvable action, except for the unsatisfactory manufacturing aspects, ODE or OIVD will issue an "Approvable Pending GMP" letter. This letter stops the review clock for the PMA.

The applicant should reply to the correspondence from FDA (i.e., deficiency, approvable pending GMP, Warning or Untitled Letter) completely and thoroughly. A response to a deficiency, Warning or Untitled Letter begins what FDA considers a new 20 or 30 day FDA manufacturing section review period (Table 1). More than one cycle of correspondence may be needed to resolve deficiencies. Once deficiencies or violations appear to have been corrected, OC/FOB may issue a new inspection assignment, if needed, beginning a new cycle

of review including the 45 or 60 day inspection as well as EIR completion and review by the District and OC or OIVD.

E. In summary, what is the general review cycle time for the manufacturing section and operations?

Attachment A lists the internal FDA process phases and times for domestic and foreign inspections. The inspection assignment phase and manufacturing review phase are concurrent. In order to help meet the MDUFMA PMA performance goals, FDA plans to complete its review of the manufacturing information and the inspection within a total cycle time of approximately 140 days for a nonexpedited PMA and 120 days for an expedited PMA.

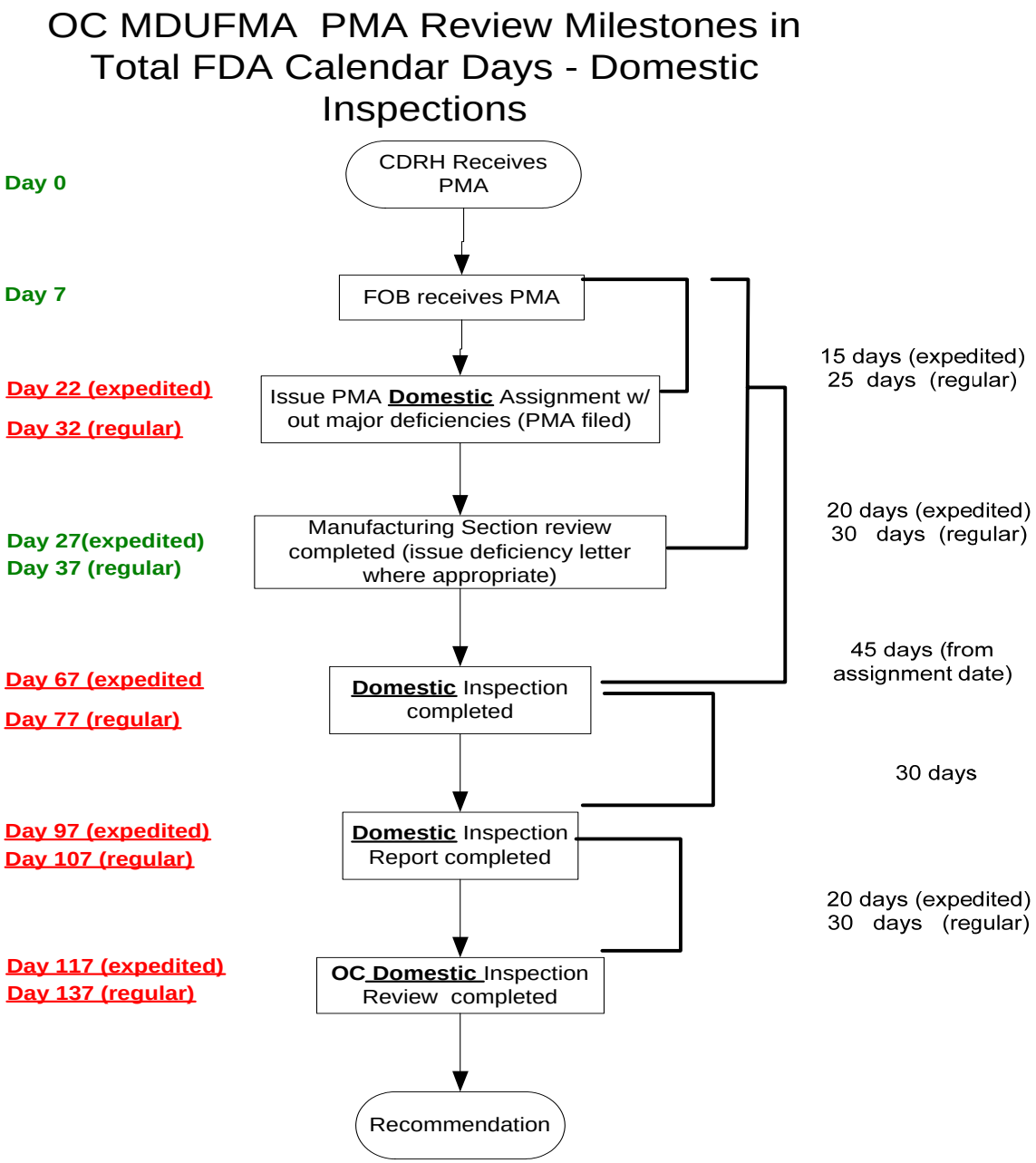
F. What are the most common factors that delay the review of a PMA manufacturing section or delay the inspection process?

- When OC or OIVD issues a manufacturing section deficiency letter to a PMA applicant, a timely and thorough response facilitates the review process. Until OC or OIVD receives the requested information, the review of the manufacturing section remains on hold and no inspection will be scheduled.

- When a timely response is not received to real-time questions during the manufacturing section review, FDA may issue a manufacturing section deficiency letter and/or an approvable pending GMP letter. Further information regarding the agency's plans for the issuance of an approvable pending GMP letter will be provided in a future revision to the guidance entitled, "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Performance Assessment."

- The manufacturing process should be in operation as soon as possible after PMA submission. If the manufacturing process described in the PMA is not in operation, FDA cannot make an adequate assessment of the Quality System. Rescheduling a PMA inspection may result in further delays of the FDA review of the PMA's manufacturing section and operations and result in an approvable pending GMP letter.

Attachment A
Process Flow Charts



Attachment A
Process Flow Charts

OC MDUFMA PMA Review Milestones in Total FDA Calendar Days - *Foreign Inspections*